REMARKS

STATUS OF THE CLAIMS

Claims 66-71 and 125-128 were pending. By amendment herein, claims 125-128 have been amended for proper antecedent basis. Thus, claims 66-71 and 125-128 are pending as shown above.

REJECTIONS WITHDRAWN

The rejection of claims 66-71 and 125-128 under 35 U.S.C. § 102(b) was not reiterated and is therefore considered withdrawn.

35 U.S.C. § 112, 2ND PARAGRAPH

Claims 125-128 were rejected under 35 U.S.C. § 112, 2nd paragraph as allegedly indefinite for reciting the "polynucleotide of claim ..." rather than the "library of claim ... ." (Office Action, pages 6-7).

Applicants submit that the foregoing amendments to claims 125-128 obviate the rejection.

35 U.S.C. § 103(a)

Claims 66-71 and 125-128 were newly rejected under 35 U.S.C. § 103(a) as allegedly obvious over Clontech in view of U.S. Patent No. 5,635,355 (hereinafter "Grosveld"). (Office Action, pages 3-6). While it was acknowledged that Clontech does not disclose a library where each and every polynucleotide has an insert that consist essentially of accessible regions of cellular chromatin, it was alleged that Grosveld provides the motivation to modify Clontech to clone regulatory sequences. *Id.*

Because the references do not teach the claimed elements, Applicants traverse the rejection and supporting remarks.

Claim 66, from which all claims directly or ultimately depend, is drawn to a library of polynucleotides in which each polynucleotide comprises an insert sequence consisting essentially of an accessible region of cellular chromatin. Moreover, the library is obtained by the specific, recited steps, including (a) contacting cellular chromatin with a probe that cleaves the chromatin

at accessible regions of cellular chromatin; (b) deproteinizing the cleaved chromatin; (c) digesting the deproteinized chromatin with a nuclease to generate a collection of polynucleotide fragments; and (d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage.

In the instant case, there is no combination of Clontech and Grosveld that teaches all the elements of the claims.

As set forth by the Board and as acknowledged by the Examiner, the claimed libraries are not taught or suggested in the Clontech Catalog because the term "consisting essentially of" excludes clones containing only non-accessible regions that would necessarily be found in the Clontech libraries (Decision on Petition, at page 5):

> We find that when the Specification is viewed as a whole it discloses that the basic and novel characteristics of the claimed polynucleotides and libraries are that they arise from, and correspond to, accessible regions of cellular chromatin. Throughout the Specification Appellants refer to methods of production of libraries which do not include only inaccessible regions of chromatin and to polynucleotides and libraries corresponding to accessible regions of chromatin. (See e.g., Spec. 4:27-32 and Spec. 27:13-34.). Thus, we do not agree with the Examiner that on the record before us the term "consisting essentially of" should be construed as equivalent to the term "comprising."

Thus, as determined by the Board and acknowledged by the Examiner, Clontech does not teach all the elements of the claimed libraries. Moreover, this establishes that the process steps recited in obtaining the claimed libraries impart structural differences in the claimed libraries as compared to Clontech's.

It is axiomatic that to establish *prima facie* obviousness of a claimed invention, all of the claim features must be taught or suggested by the cited references. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Accordingly, in order to establish a *prima facie* case of obviousness, Grosveld must provide what is missing from the Clontech reference in terms of the claimed elements, namely by teaching libraries consisting essentially of inserts corresponding to accessible regions of cellular chromatin, which libraries are obtained by the recited steps.

In point of fact, there are absolutely no teachings whatsoever in Grosveld regarding libraries as claimed. The claimed libraries consist essentially of inserts corresponding to accessible regions and are obtained by specific cloning steps. By contrast, Grosveld states that

hypersensitive sites may be "mapped" (col. 7, lines 59-63). The only cloning referred to in Grosveld involves construction of a single target sequence that, in certain cells, comprises a DNAse hypersensitive site. Cloning of "the target sequence" (*i.e.*, a single sequence) into a vector results in the production of multiple copies of the same sequence, or what is normally referred to in the art as a clone. It does not produce a library of polynucleotide sequences in the same way that a building containing multiple copies of the same book for loan would not be considered a library. Accordingly, like Clontech, Grosveld does not teach the claimed libraries.

Furthermore, Grosveld not only fails to teach anything about libraries, this reference also fails to teach the recited method steps required to obtain these libraries. In particular, claim 66 specifies that a cellular chromatin is first contacted with a probe that cleaves accessible regions of cellular chromatin (claim 66, step (a)). Subsequently, the cleaved chromatin is deproteinized (claim 66, step (b)) and the deproteinized chromatin digested with a nuclease to generate a collection of polynucleotide fragments (claim 66, step (c)). The polynucleotide fragments are then selectively cloned as inserts into a library (claim 66, step (d)).

By contrast, Grosveld teaches that, in one case, nuclei were treated with DNase I (first enzyme), then deproteinized DNA was recut with *Asp*718 or *Bgl*II (second enzymes). *See,* col. 8, lines 17-32 of Grosveld. In a second case, nuclei were treated with DNase I (first enzyme), and deproteinized DNA was recut with *Bam*HI (second enzyme). See, Grosveld, col. 8, lines 34-41. However, none of these fragments (containing one end generated from the probe) in Grosveld were cloned. In the only portions of Grosveld referring to cloning, the DNA fragments that were cloned were an *Xba*I-*Xba*I fragment (containing DNaseI HS1), a *Hind*III-*Hind*III fragment (containing DNaseI HS2), a *Asp*718-*Sal*I fragment rendered blunt-ended (containing DNaseI HS3) and a partial *Sac*I fragment (containing DNaseI HS4). *See,* Grosveld, col. 15, lines 16-31. As none of these fragments which were cloned by Grosveld correspond to a DNaseI-*Asp*718 fragment, a DNaseI-*Bgl*II fragment or a DNaseI-*Bam*HI fragment, Grosveld fails to supply what is missing from Clontech as this does not teach or suggest libraries consisting essentially of accessible regions, obtained by the recited steps, including selectively cloning of a fragment having one end generated by probe cleavage of cellular chromatin at accessible regions.

Finally, it is again noted that, since Grosveld is directed at obtaining integration site-independent gene expression using DNase hypersensitive sites, it is aimed at a different

problem than that of the presently-claimed subject matter, which is directed to libraries consisting of essentially of accessible regions obtained from genome-wide isolation and purification of accessible regions. Previously, regulatory sequences could not be isolated because they were destroyed in the process of being identified. Accordingly, there is no motivation for one of skill reading Grosveld or Clontech to look for guidance in the other reference on how to obtain a library consisting essential of accessible regions by simultaneously isolating and purifying these accessible regions from a cell. Moreover, as noted above, as the recited steps of obtaining the library that result in a library consisting essentially of accessible regions not taught in the art, the claimed libraries are structurally distinguishable from those of the art based on the methods by which they are produced.

Thus, like Clontech, Grosveld fails to teach or suggest a library consisting essentially of accessible regions that have been cloned from a collection of polynucleotides that have been produced by contacting nuclei with a first enzyme, deproteinizing and contacting the deproteinized DNA with a nuclease, and cloning the resulting fragments, as claimed. The properties of the claimed libraries and steps in obtaining these libraries are precisely defined -- in the claims themselves, not in the references. Because Clontech fails to disclose the claimed libraries obtained by the claimed steps and because Grosveld fails to disclose any type of library at all, let alone libraries consisting essentially of accessible sequences prepared as recited in the claims, there is no combination of Grosveld and Clontech that can render any of the pending claims obvious.

Accordingly, a *prima facie* case of obviousness cannot be established and Applicants respectfully request that the rejection of these claims as allegedly obvious over the cited references be withdrawn, and that these claims be allowed.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Respectfully submitted,

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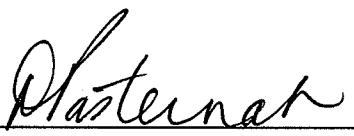
By: 

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